Zika Virus Disease and Infection, Non-Congenital

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Merlin reporting code = 06010 Zika Virus Disease and Infection, Non-Congenital
Case report form (CRF): *Florida Confidential Vector-borne Disease Infection CRF*
MERLIN EXTENDED DATA REQUIRED

Background

Zika virus (ZIKV) is an emerging mosquito-borne virus that has spread rapidly across the Americas in 2015 and 2016. Only about 1 in 5 people infected with Zika virus are symptomatic and some patients may not have fever. ZIKV disease, dengue fever, and chikungunya fever are difficult to differentiate clinically. It is also important to note that co-infections with these viruses can occur. Subsequent investigations have demonstrated vertical transmission of ZIKV to the fetus in pregnant women. These in utero infections have been associated with the potential for devastating outcomes including microcephaly, other central nervous system abnormalities, and spontaneous abortions. There is also an association with ZIKV infection and post-infection Guillain-Barré syndrome (GBS).

Clinical criteria for diagnosis

A person with one or more of the following not explained by another etiology:

- Clinically compatible illness that includes one or more of the following:
  - Fever (measured or reported), or
  - Rash, or
  - Arthralgia, or
  - Conjunctivitis;

OR

- Complication of pregnancy including one of the following:
  - Fetal loss or
  - Fetus or neonate with congenital microcephaly, congenital intracranial calcifications, other structural brain or eye abnormalities, or other congenital central nervous system-related abnormalities including defects such as clubfoot or multiple joint contractures;

OR

- GBS meeting Brighton Collaboration level 1, 2, or 3 or other neurologic manifestations.

Laboratory criteria for diagnosis

Confirmatory:

- Detection of ZIKV by culture, viral antigen, or viral RNA in serum, CSF, tissue, or other specimen (e.g., urine, whole blood, amniotic fluid, semen)

OR

- All of the following:
  - Positive enzyme immunosorbent assay (EIA) or immunofluorescent assay (IFA) test for ZIKV IgM antibodies in serum or CSF, **and**
  - Positive neutralizing antibody titers by plaque reduction neutralization test (PRNT) against ZIKV, **and**
  - Negative neutralizing antibody titers by PRNT against dengue virus (DENV) or other flaviviruses endemic to the region where exposure occurred.

Presumptive:

For sporadic or index cases acquired locally via mosquito exposure:

- Positive EIA or IFA test for ZIKV IgM antibodies in serum or CSF, **and**
- Positive neutralizing antibody titers by PRNT against ZIKV, and
- Absence of positive IgM for other flaviviruses.

For cases in pregnant women:

- Positive, equivocal, or indeterminate EIA or IFA test for ZIKV IgM antibodies in serum or CSF **and**
- Positive neutralizing antibody titers by PRNT against ZIKV.

For all other cases including cases acquired locally via mosquito exposure after epidemiologic linkage or transmission in an area has been established:

- All of the following:
  - Positive, equivocal, or indeterminate EIA or IFA test for ZIKV IgM antibodies in serum or CSF **and**
  - Positive neutralizing antibody titers by PRNT against ZIKV;

OR

- All of the following:
  - Positive EIA or IFA test for ZIKV IgM antibodies in serum or CSF, **and**
  - Negative, equivocal, or indeterminate for DENV IgM antibodies or IgM antibodies to other flaviviruses endemic to the region where the exposure occurred, **and**
  - No PRNT performed;

OR

- Both of the following:
  - Seroconversion from negative for ZIKV IgM antibodies in an acute-phase specimen to positive for ZIKV IgM antibodies in a convalescent-phase specimen by EIA or IFA in serum or CSF **and**
  - Negative, equivocal, or indeterminate for DENV IgM antibodies or IgM antibodies to other flaviviruses endemic to the region where the exposure occurred.

OR

- All of the following:
  - Positive EIA or IFA test for ZIKV IgM antibodies in serum or CSF, **and**
  - Negative DENV PCR, **and**
  - Negative, equivocal, or indeterminate for DENV IgM antibodies, **and**
  - Seroconversion from negative for DENV IgG antibodies in an acute-phase specimen to positive for DENV IgG antibodies in a convalescent-phase specimen.

OR

- All of the following:
  - Positive EIA or IFA test for ZIKV IgM antibodies in serum or CSF, **and**
  - No PRNT performed, **and**
  - No DENV testing performed.

Supportive:

- Positive neutralizing antibody titers by PRNT against ZIKV;

OR

- All of the following:
  - Positive EIA or IFA test for ZIKV IgM antibodies in serum or CSF, **and**
  - Positive for DENV IgM antibodies or IgM antibodies to other flaviviruses endemic to the region where the exposure occurred, **and**
  - No PRNT performed;

OR

- Both of the following:
    - Equivocal or indeterminate EIA or IFA test for ZIKV IgM antibodies in serum or CSF **and**
    - No PRNT performed;

OR

- All of the following:
    - Negative EIA or IFA test for ZIKV IgM antibodies in serum or CSF, **and**
    - Positive for DENV IgM antibodies or IgM antibodies to other flaviviruses endemic to the region where the exposure occurred, **and**
    - Positive neutralizing antibody titers by PRNT against ZIKV.

Epidemiological criteria for diagnosis

One or more of the following:

- Resides in or recent travel to an area with known ZIKV transmission, or
- Sexual contact with a confirmed or probable case of ZIKV infection or person with recent travel to an area with known ZIKV transmission, or
- Receipt of blood or blood products within 30 days of symptom onset, or
- Receipt of organ or tissue transplant within 30 days of symptom onset, or
- Association in time and place with a confirmed or probable case, or
- Likely vector exposure in an area with suitable seasonal and ecological conditions for potential local vectorborne transmission.

Case classification

Confirmed:

Zika virus disease:
A clinically compatible illness in a person with confirmatory laboratory evidence who meets the epidemiologic criteria.

Zika virus infection:
A person with confirmatory laboratory evidence who meets the epidemiologic criteria.

Probable:

Zika virus disease:
A clinically compatible illness in a person with presumptive laboratory evidence who meets the epidemiologic criteria.

Zika virus infection:
A person with presumptive laboratory evidence who meets the epidemiologic criteria.

Suspect:

Zika virus disease:
A clinically compatible illness in a person with supportive laboratory evidence who meets the epidemiologic criteria.

Zika virus infection:
A person with supportive laboratory evidence who meets the epidemiologic criteria.

Comments

Cross-reaction with related flaviviruses (e.g., dengue, West Nile, yellow fever, Japanese encephalitis viruses) on serological tests is common and results may be difficult to interpret. Due to this cross-

reactivity, it is important to ask if there has been any lifetime travel to a flavivirus-endemic country or vaccination for yellow fever or Japanese encephalitis viruses. In addition, people with dengue infection often test positive for ZIKV IgM.

Clinicians should also consider testing for dengue and chikungunya fever for suspect cases of ZIKV disease if fever was reported. As testing capacity allows, all samples meeting the requirements for ZIKV disease PCR testing at the Bureau of Public Health Laboratories (BPHL) will also be tested for dengue and chikungunya viruses if the patient reported fever. All samples collected in the first four days of illness and meeting standard requirements for dengue and chikungunya testing will also be tested for Zika virus by PCR if travel to a ZIKV disease endemic area is reported.

Differentiating between ZIKV and DENV infections in PCR-negative patients with positive flavivirus labs

- Conjunctivitis and pruritic rash are more common with ZIKV disease than dengue fever.
- Thrombocytopenia and leukopenia are more common and severe in cases of dengue fever compared to ZIKV disease.
- ZIKV is not known to cause severe syndromes that can be seen with DENV (dengue hemorrhagic fever or dengue shock syndrome).
- ZIKV IgM titers are usually positive in dengue fever patients. DENV IgM titers may or may not be positive in ZIKV disease patients. IgM EIA results from BPHL are not quantitative and the values derived from this assay cannot be compared between illnesses.
- For non-PCR positive cases, dengue fever cases should be created instead of ZIKV disease cases if:
    - The clinician ordered dengue testing, did not request Zika testing, and dengue IgM was positive.
    - The clinician ordered Zika testing and Zika IgM was negative, while dengue IgM was positive.
    - PRNT testing is positive for dengue and negative for Zika.
    - For locally acquired cases, individuals that are IgM positive for both Zika and dengue will be evaluated on a case by case basis.

Acute and convalescent samples from people with infections believed to be Florida-acquired should be sent to BPHL. Acute samples from people with infections believed to be acquired outside Florida should also be sent to BPHL.